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History of OxyContin: Labeling and Risk Management Program

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Anesthetic and Life Support Drugs and Drug Safety and Risk
Management Advisory Committees, November 13 & 14, 2008

Summary of Presentation

- **History of Oxycontin**
- **Important Labeling Changes**
- **Risk Management**



OxyContin: Approval

- **OxyContin was approved on December 12, 1995.**
 - **Launched in 1996**
- **Approval occurred when:**
 - **There was increasing recognition that many patients with pain are inadequately treated**
 - **Diversion and abuse of prescription drugs was increasing**

OxyContin: Initial product labeling

- **Schedule: CII**
- **Strengths: 10, 20, and 40 mg controlled-release tablets**
- **Clinical trials:**
 - **Both cancer and non-cancer pain populations**
 - **Use in opioid-naïve patients**
 - **Equivalence and open-label studies**



OxyContin: Initial product labeling

- **Indication:**
 - **“For the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days.”**

OxyContin: Initial labeling

- **Warnings; Dosage and Administration:**
 - “OxyContin tablets are to be swallowed whole, and are not to be broken, chewed, or crushed. *Swallowing broken, chewed, or crushed OxyContin tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone.*”
- **Drug abuse and Dependence:**
 - OxyContin...is a schedule II controlled substance. Oxycodone products are common targets for both drug abusers and drug addicts. *Delayed absorption, as provided by OxyContin tablets is believed to reduce the abuse liability of a drug.*”



OxyContin: supplemental NDAs

- 80-mg tablet approved in 1996; 160-mg tablet in 2000
- Notable changes to the product label:
 - Description:
 - 80-mg and 160-mg tablets to be used only in opioid tolerant patients.
 - Precautions; Dosage and Administration:
 - *OxyContin 80 [160] mg tablets are for use only in opioid tolerant patients requiring daily equivalent dosages of 160 [320] mg or more. ... Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences.*



Increased OxyContin availability

- **Purdue implemented an aggressive marketing campaign:**
 - **Primary care providers**
 - **Use in non-cancer pain**
 - **Musculoskeletal pain; post-operative pain**
 - **Use as “first-line” therapy for chronic pain**
 - **Physician-directed advertising**
 - **Medical journals; conferences; video**
- **Certain promotional claims cited by DDMAC**

2000: Initial reports of OxyContin abuse and diversion

- **Increasing media and state reports of abuse and diversion of OxyContin:**
 - **Crushing of tablets**
 - **Oral, inhalation, injection administration**
 - **Adverse events included addiction, withdrawal and fatalities**
- **Prominently affected areas:**
 - **Appalachian states**
 - **Kentucky, Virginia, W. Virginia, Pennsylvania**
 - **Maine; Ohio**
- **Involved recreational drug users, teenagers, pain patients**



OxyContin abuse and diversion:

Possible contributing factors

- **Drug Substance**
 - Recent evidence suggests that oxycodone may be more reinforcing than morphine
- **Product formulation**
 - High oxycodone content
 - Although it was initially believed that the PK characteristics of a CR formulation would reduce the reinforcing properties, experience has shown that defeat of the CR mechanisms is associated with abuse

OxyContin abuse and diversion:

Possible contributing factors

- **Increased drug availability**
 - Increased prescribing of controlled prescription drugs for pain
 - Medical community more accepting of the use of opioids to treat pain
 - Purdue's strong marketing strategy
- **Product labeling**
 - Warning against crushing may have alerted abusers to a method for misuse
 - Label language suggesting that OxyContin had lower abuse potential may have impacted product use or prescribing

OxyContin abuse and diversion: Initial Agency and company actions

- **Purdue:**
 - Formed a response team to evaluate problem of abuse/diversion in Maine
 - Contacted the Agency about the problems (Mar 2001)
 - Elected to discontinue marketing of the 160 mg tablet
- **FDA:**
 - Requested additional information regarding OxyContin abuse
 - Reviewed available data to
 - Assess for any relationship between OxyContin abuse/misuse and adverse events
 - Determine prescribing patterns of OxyContin
 - Met with Purdue to discuss the issues (April 2001)



OxyContin abuse and diversion: Initial Agency and company actions

- **Risk Management Plan**
 - **August 2001**
 - **Key features**
 - **Education and outreach**
 - **Labeling**
 - **Surveillance**
 - **Intervention**



Changes to OxyContin Label

- **Addition of a Boxed Warning**
 - Calls attention to the potential for abuse, misuse and diversion of the product.
 - Highlights the proper treatment population.
- **CLINICAL TRIALS section**
 - Restricted to the single adequate and well-controlled clinical trial.
- **INDICATIONS section revised to reflect the appropriate patient population.**



Changes to OxyContin Label

- **INDICATIONS:**
 - OxyContin tablets are... indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.
 - OxyContin is not intended for intermittent dosing or as a prn analgesic.
 - OxyContin is not indicated for pain in the immediate post-operative period if the pain is mild or not expected to persist...

Changes to OxyContin Label

- **Expanded WARNINGS section**
 - Warns against breaking, crushing, or chewing the tablets
 - Highlights the potential for misuse, abuse, and diversion of OxyContin
 - Specifies the potential adverse events associated with OxyContin misuse and abuse
- **Deleted:** language regarding reduced abuse liability with a CR formulation.

OxyContin: Public Discussions

January 30 & 31, 2002

- **Advisory Committee meeting to discuss:**
 - **Opioid analgesic use and development.**
 - **Use of opioid analgesics in pediatric patients.**
 - **Abuse and misuse of opioid analgesics.**
- **Notable conclusions:**
 - **Abuse of opioid analgesics is a considerable public health problem.**
 - **However, opioid analgesics are an essential component of pain management.**
 - **Any RMP that restricts opioid treatment may prevent their appropriate utilization.**



OxyContin: Public Discussions

September 9 & 10, 2003

- **Advisory Committee meeting to discuss:**
 - RMPs for opiate analgesic drug products
 - Particular attention to modified-release products
 - Abuse liability of and RMP for Palladone (extended-released hydromorphone)
- **Key conclusions: RMP should include -**
 - Appropriate prescriber education
 - Surveillance of misuse, abuse, diversion
 - Assessment of the source(s) of diverted drugs
 - Assessment of the RMP's impact on opioid prescribing practices



OxyContin: Public Discussions

May 5, 2008

- Advisory Committee meeting to discuss: OxyContin reformulation
 - Tamper resistant properties
 - Adequacy of the testing methods
 - Impact on abuse, misuse and diversion
 - Changes to the product label
 - RMP
- Notable conclusions:
 - Available data are not adequate to support tamper-resistance claims
 - Inclusion of the new physicochemical properties in the label may result in false security and adversely impact addiction and overdose
 - RMP: directed at the entire opioid class, targeted education, restricted indication



OxyContin: Public Discussions

November 13, 2008

- Advisory Committee meeting to discuss: Remoxy XRT
 - Adequacy of tools to assess for abuse, misuse and diversion
 - Inclusion of new information in product label
 - Physicochemical attributes and associated risk/benefits
 - Data suggesting reduced risk for abuse and misuse
- Notable conclusions:
 - All available tools have limitations: need to define minimum standards for assessment of temper resistant qualities
 - Available data are not adequate to support tamper-resistance claims
 - Physicochemical properties described in the label may result in false security and adversely impact addiction and overdose



REMS

- **New authorities granted under FDAAA to implement Risk Evaluation and Mitigation Strategies**
- **FDA may require REMS if it is necessary to ensure that benefits of drug outweigh the risks**

OxyContin: Risk Management

- **Current Proposal for Extended-Release Opioid Class REMS**
 - **All extended-release oral opioids**
 - **Methadone**
 - **Transdermal fentanyl**
 - **OTFC not included**



OxyContin: Risk Management

- **Status of Opioid REMS**
 - **Series of stakeholder meetings (over past several months) to discuss design and implementation of REMS**
 - **Federal Register Notice for Comments**
 - **Agency Working Group to assemble and analyze input**

OxyContin: Risk Management

- **Proposed REMS**
 - **Medication Guide**
 - **Elements to Assure Safe Use**
 - **Implementation System**
 - **Timetable for Submission of Assessments**



OxyContin: Risk Management

- **Interim REMS**
 - **Medication Guide**
 - **Communication Plan**
 - **Dear HCP, Dear Pharmacist**
 - **Brochure**
 - **Timetable for submission of assessments**



Current status

- Over the years, FDA and Purdue have negotiated numerous revisions to strengthen the product labeling and the RMP.
- However, multiple indices show that abuse and diversion of OxyContin continue to be significant public health issues.
- Availability of a ER oxycodone product with reduced abuse liability is desirable.
- The impact of a “less abusable” formulation of Oxycontin on abuse is unknown
- Epidemiologic studies of abuse will be required to assess the impact



Epidemiological Findings of Drug Misuse/Abuse in the United States: Oxycontin

Summary of data previously presented at the Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committees, May 5, 2008

Catherine Dormitzer, PhD, MPH
Division of Epidemiology (DEPI)
Office of Surveillance and Epidemiology (OSE)

Overview

- Data previously presented at Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committees on May 5, 2008
- Findings from TEDS
- Findings from NSDUH
- Findings from DAWN
- Methods used to calculate Drug Abuse Ratios
- Summary of calculations
- Conclusions

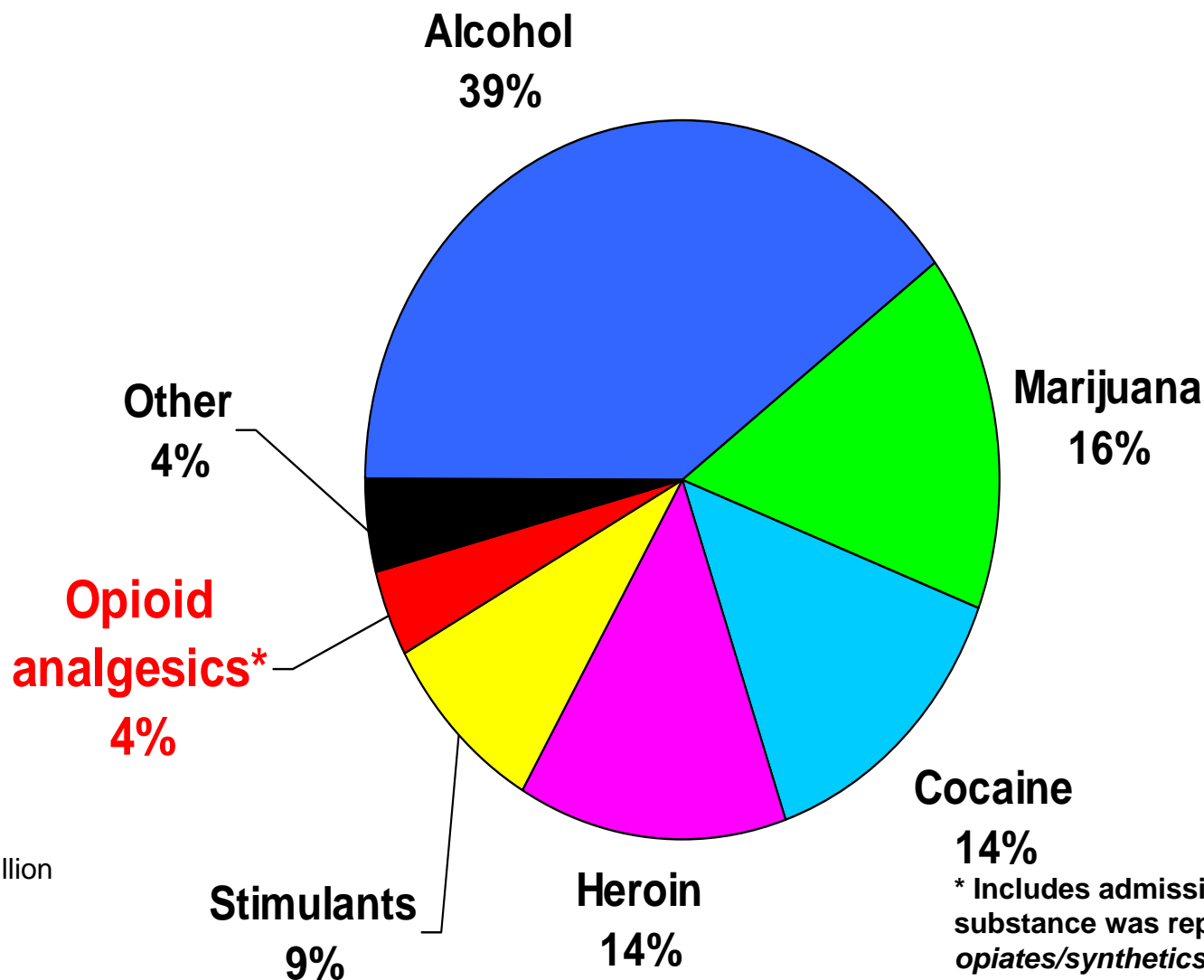
Treatment Episode Data Set (TEDS)

- Client-level information on treatment admissions
- Collected by States and reported to SAMHSA
- Primarily from facilities receiving public funds
- Estimated coverage – 80%
- 1.8 million admissions annually
- Ratios were not calculated using TEDS data

TEDS: Data Elements & Limitations

- Demographic variables
- Drug use history
 - top 3 substances of abuse at admission
 - route of administration
 - frequency of use
 - age at first use
- Treatment variables
- Drugs of abuse reported in “generic” categories, not specific brand names or formulations
- All States report on “opiates other than heroin” as a group
- Only 16 States report on specific opioid analgesics

Treatment Admissions by Primary Substance: 2006



N = 1.8 million

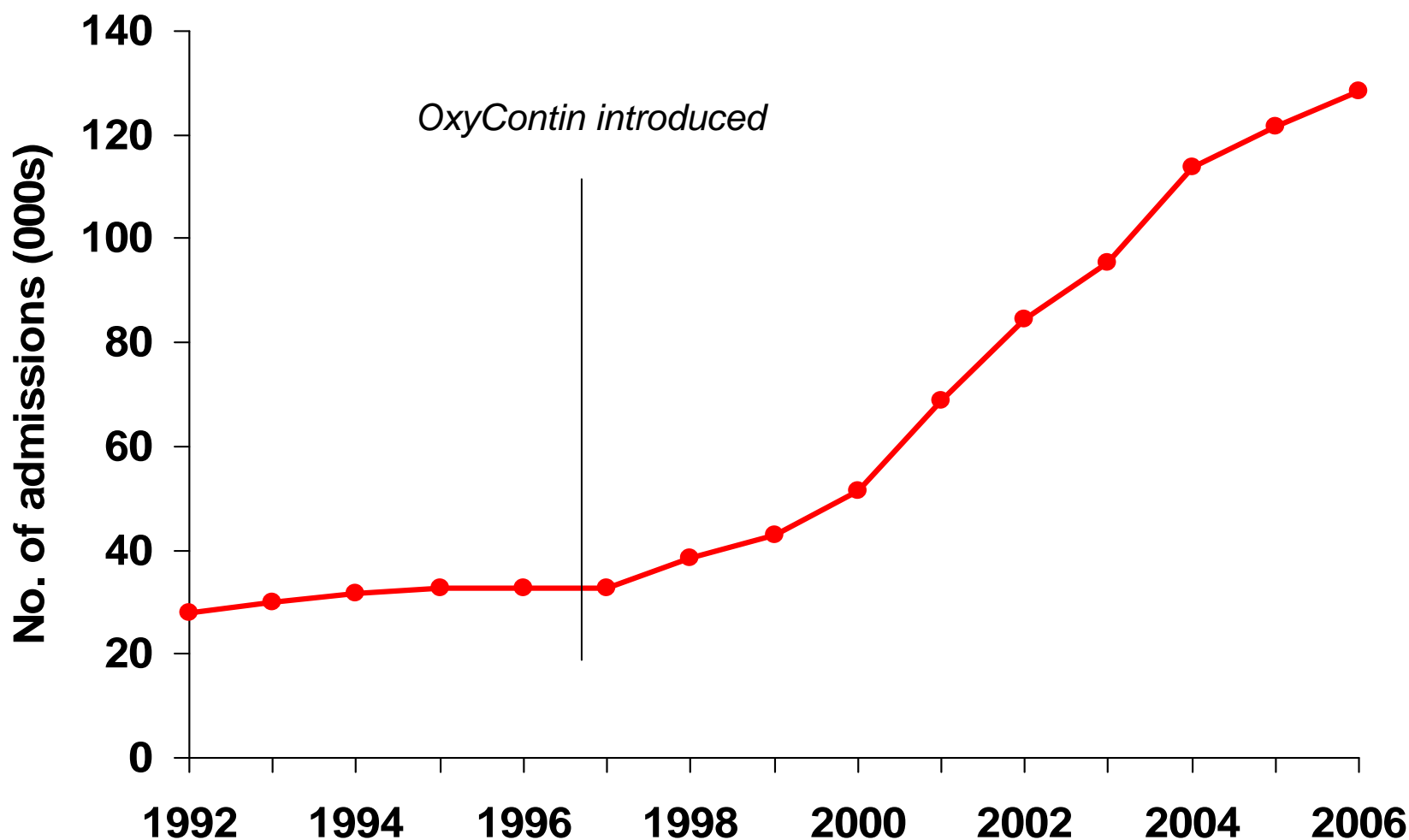
* Includes admissions where primary substance was reported as *Other opiates/synthetics*. Excludes 5 admissions for non-prescription use of methadone.

Admissions Involving Specific Opioid Analgesics¹: 2006

Oxycodone	15,300
Codeine	1,200
Hydrocodone	900
Hydromorphone	900
Propoxyphene	162
Meperidine	80
Pentazocine	30
Tramadol	50
Other opiates or synthetics	33,100

¹Data submitted by 16 States: AL, HI, ID, KY, MD, ME, MO, MS, ND, NH, NJ, NM, NV, NY, OH, SD

TEDS -- Treatment Admissions Involving Opioid Analgesics¹; 1992-2006



¹ Includes admissions where primary, secondary, or tertiary substance was reported as *Other opiates/synthetics*. Excludes admissions for non-prescription use of methadone.

National Survey on Drug Use and Health (NSDUH)

- Representative nationally and in each State
- Civilian, noninstitutional population, age 12+
- Face-to-face interview, 1 hour
- Computer-assisted, mainly self-administered
- 67,500 respondents each year
- Survey changed in 1999 and in 2002, creating breaks in trend
- Response rates (2006):
 - 91% of Households selected
 - 74% of Persons selected within households (85% for youth, 73% for adults)

Nonmedical Prescription Drug Use: NSDUH Definition

“Not prescribed for you”

OR

“You took the drug only for the
experience or feeling it caused”

(Excludes OTC)

“PILL CARDS”

Drug groups above the red line are asked separately

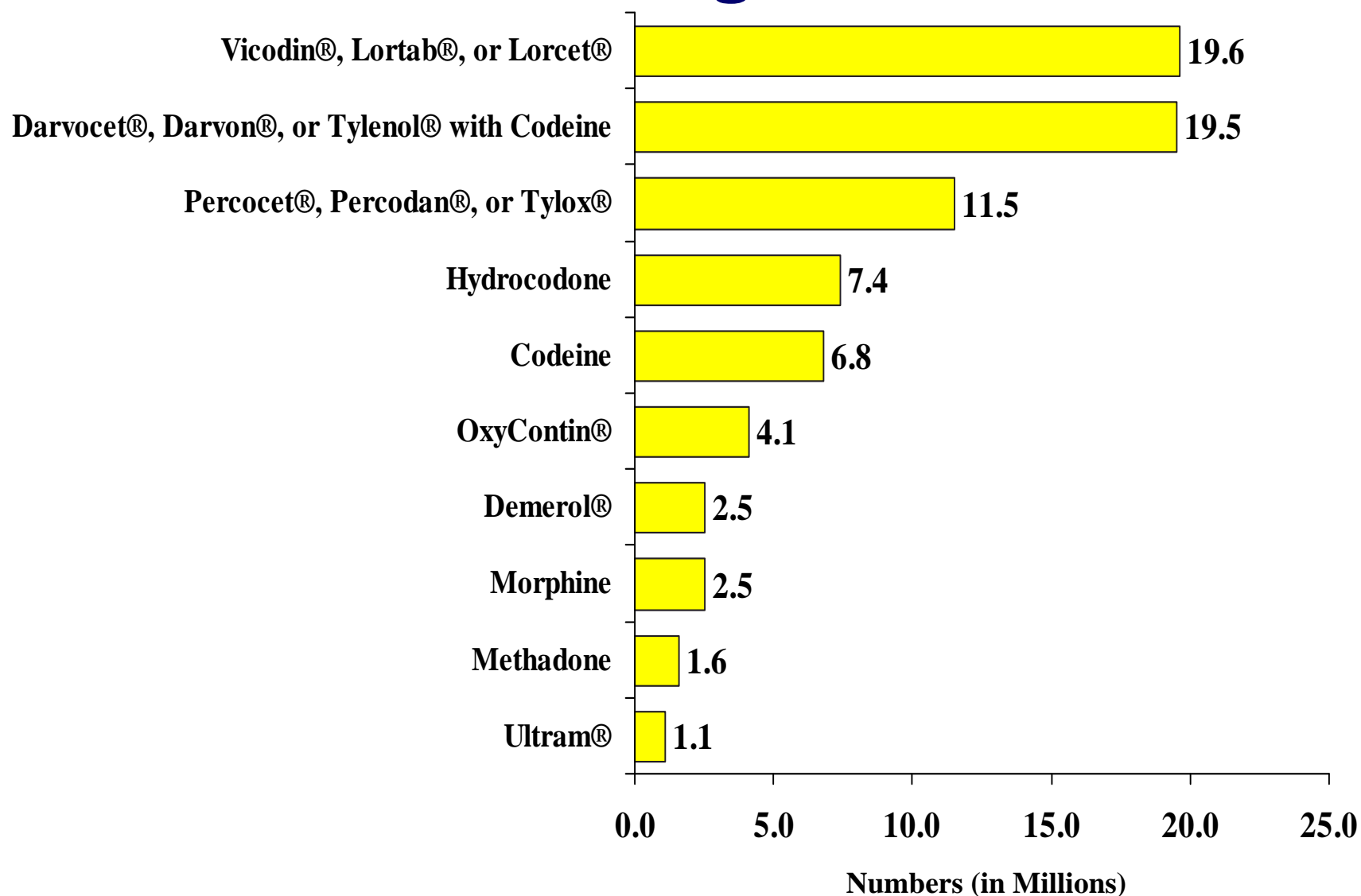
Drug groups below the red line are asked in tandem with followup to identify which one(s)

Any other drugs in TC are specified by write-in.

CARD A Pain Relievers

<p>1</p> <p>Darvocet-N®</p> <p>Darvon®</p> <p>Tylenol® with Codeine</p>	<p>2</p> <p>Percocet®</p> <p>Percodan®</p> <p>Tylox®</p>	<p>3</p> <p>Vicodin®</p> <p>Lortab®</p> <p>Lorcet®/Lorcet Plus®</p>
<p>4</p> <p>Codeine</p>	<p>9</p> <p>Hydrocodone</p>	<p>14</p> <p>Propoxyphene</p>
<p>5</p> <p>Demerol®</p>	<p>10</p> <p>Methadone</p>	<p>15</p> <p>SK-65®</p>
<p>6</p> <p>Dilaudid®</p>	<p>11</p> <p>Morphine</p>	<p>16</p> <p>Stadol®</p>
<p>7</p> <p>Fioricet®</p>	<p>12</p> <p>OxyContin®</p>	<p>17</p> <p>Talacen®</p>
<p>8</p> <p>Fiorinal®</p>	<p>13</p> <p>Phenaphen® with Codeine</p>	<p>18</p> <p>Talwin®</p>
		<p>19</p> <p>Talwin® NX</p>
		<p>20</p> <p>Tramadol</p>
		<p>21</p> <p>Ultram®</p>

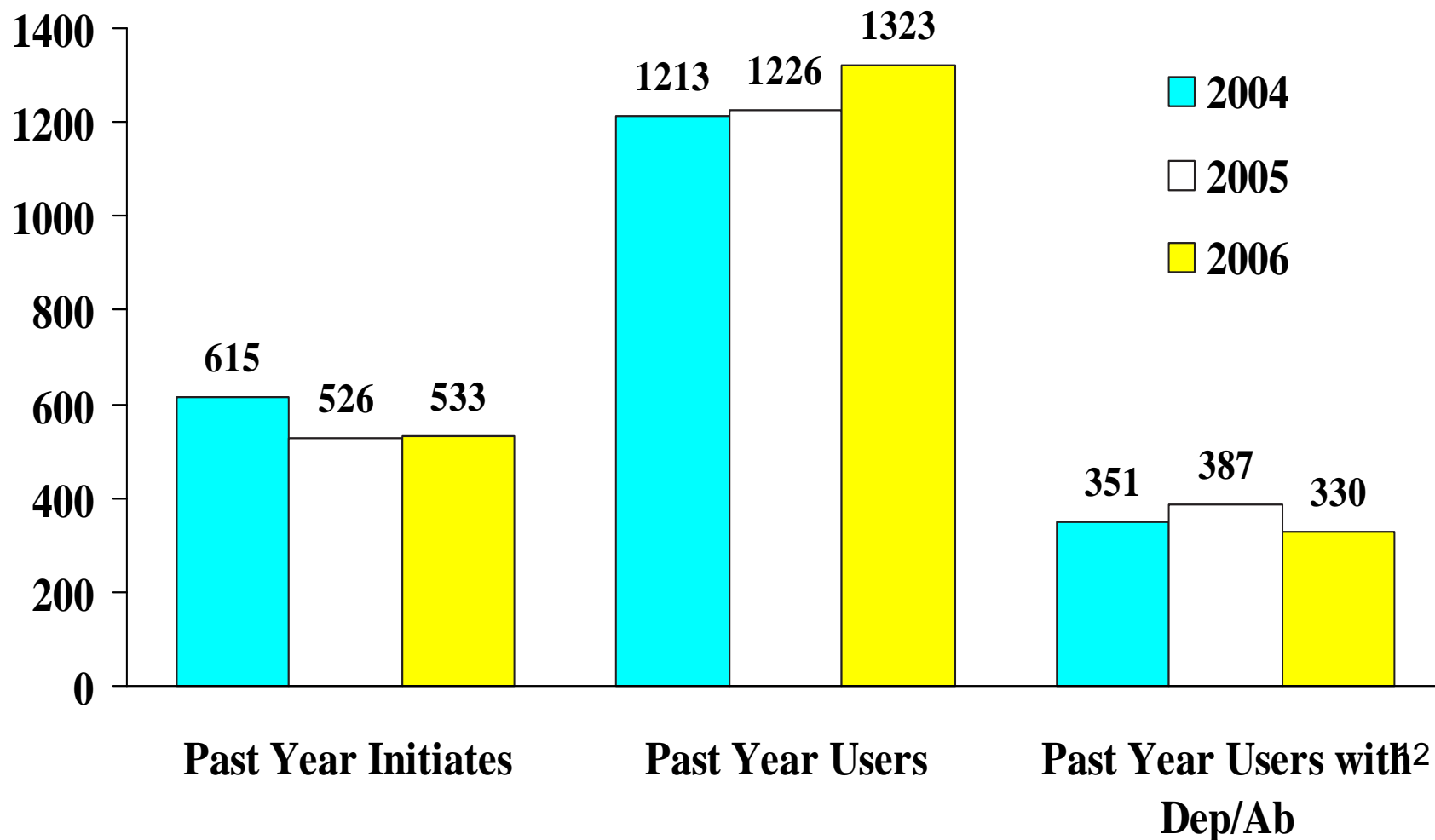
Lifetime Nonmedical Use of Selected Pain Relievers, Age 12 or Older: 2006





Past Year Indicators of Nonmedical Use of OxyContin, 12 and Older: 2004-2006

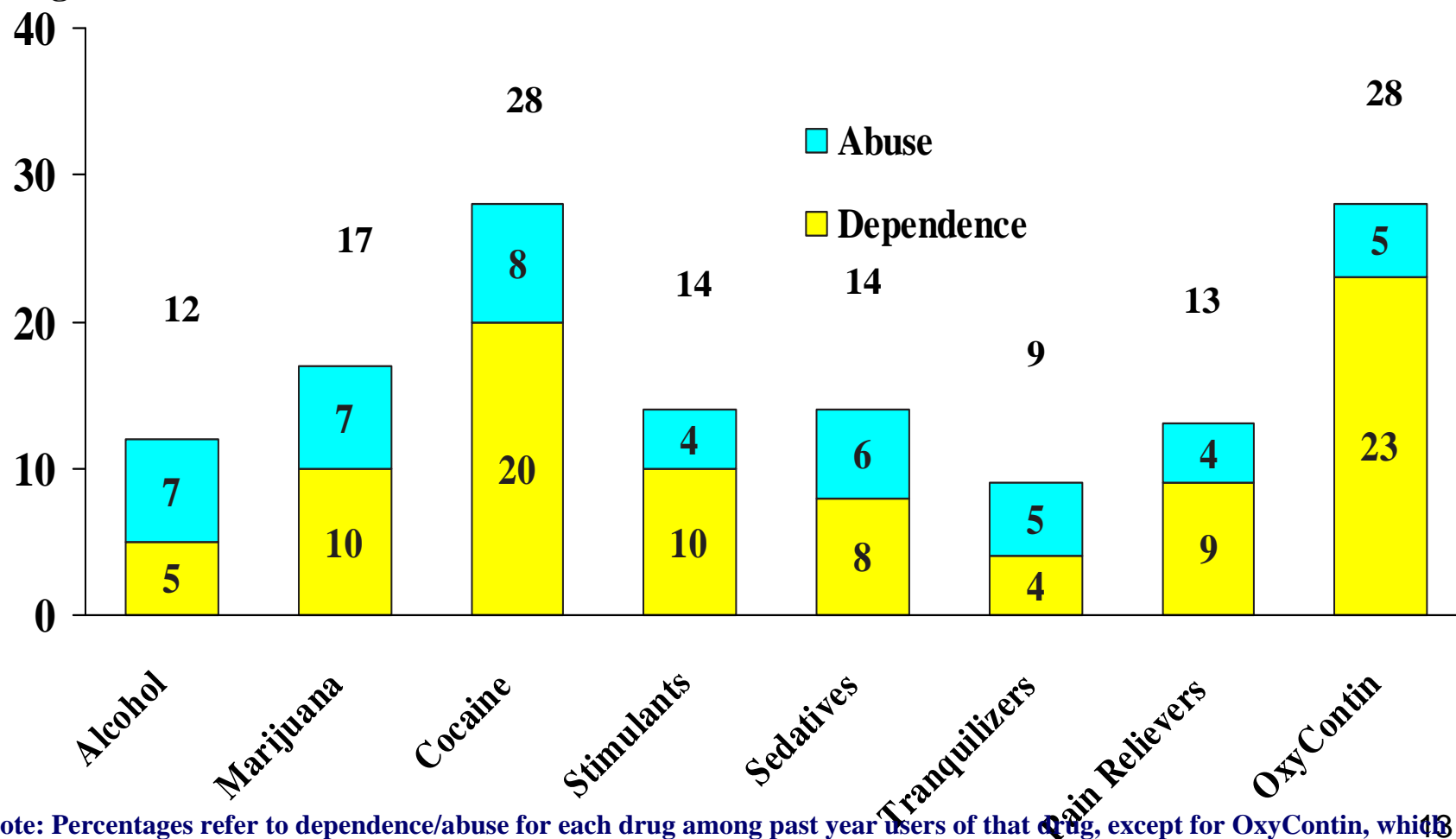
Number in Thousands





Dependence and Abuse Among Past Year Users of Selected Substances, Ages 12+: Annual Averages, 2004-2006

Percentage of Past Year Users



Note: Percentages refer to dependence/abuse for each drug among past year users of that drug, except for OxyContin, which reflects pain reliever dependence/abuse among past year OxyContin users.

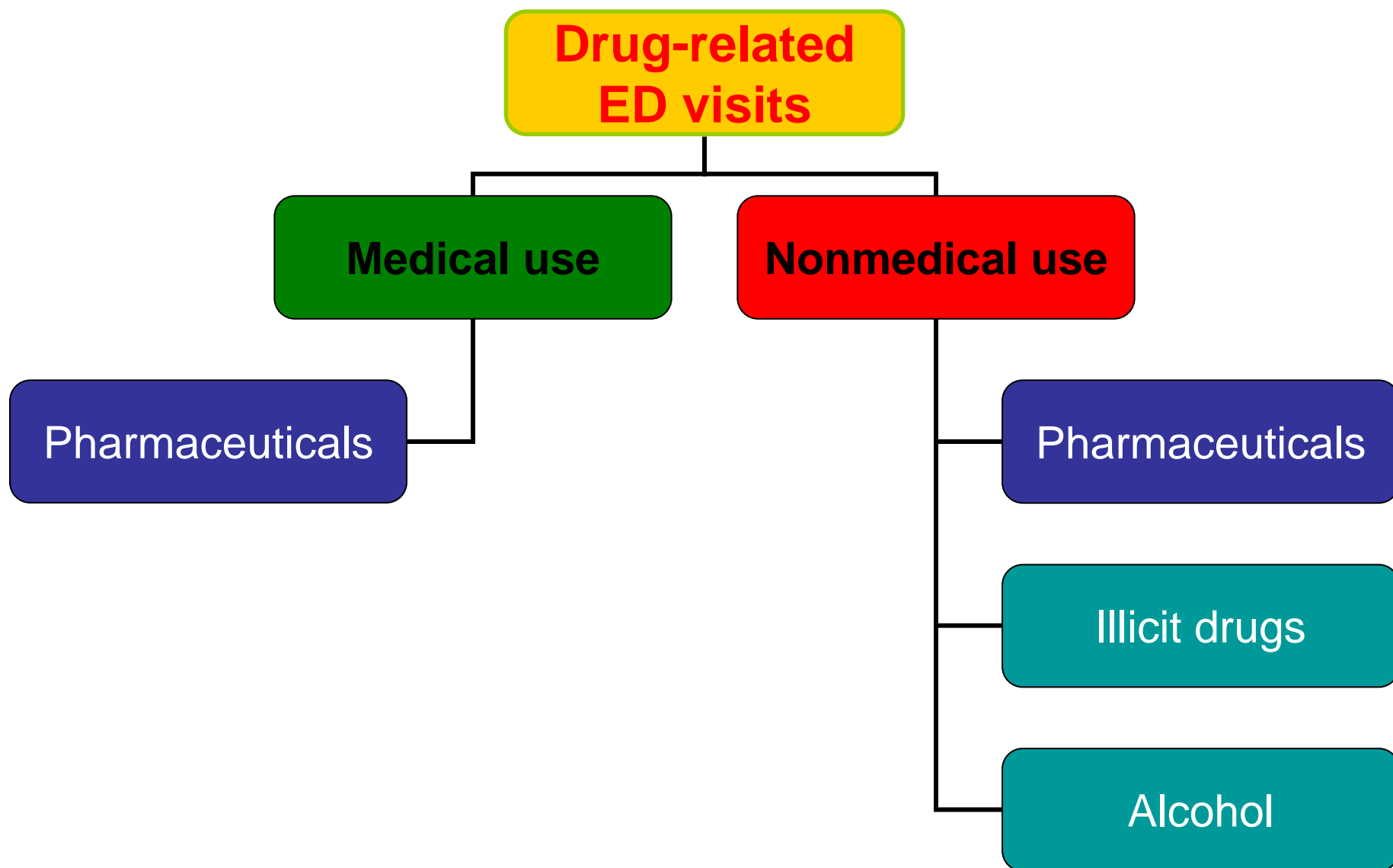
Drug Abuse Warning Network -- DAWN

- Stratified probability sample of hospitals
 - Short-term, general, nonFederal hospitals with 24-hour emergency departments (EDs)
 - Oversample areas
 - Remainder area
- National estimates account for:
 - Sample design
 - Unit nonresponse
 - Partial nonresponse in responding hospital

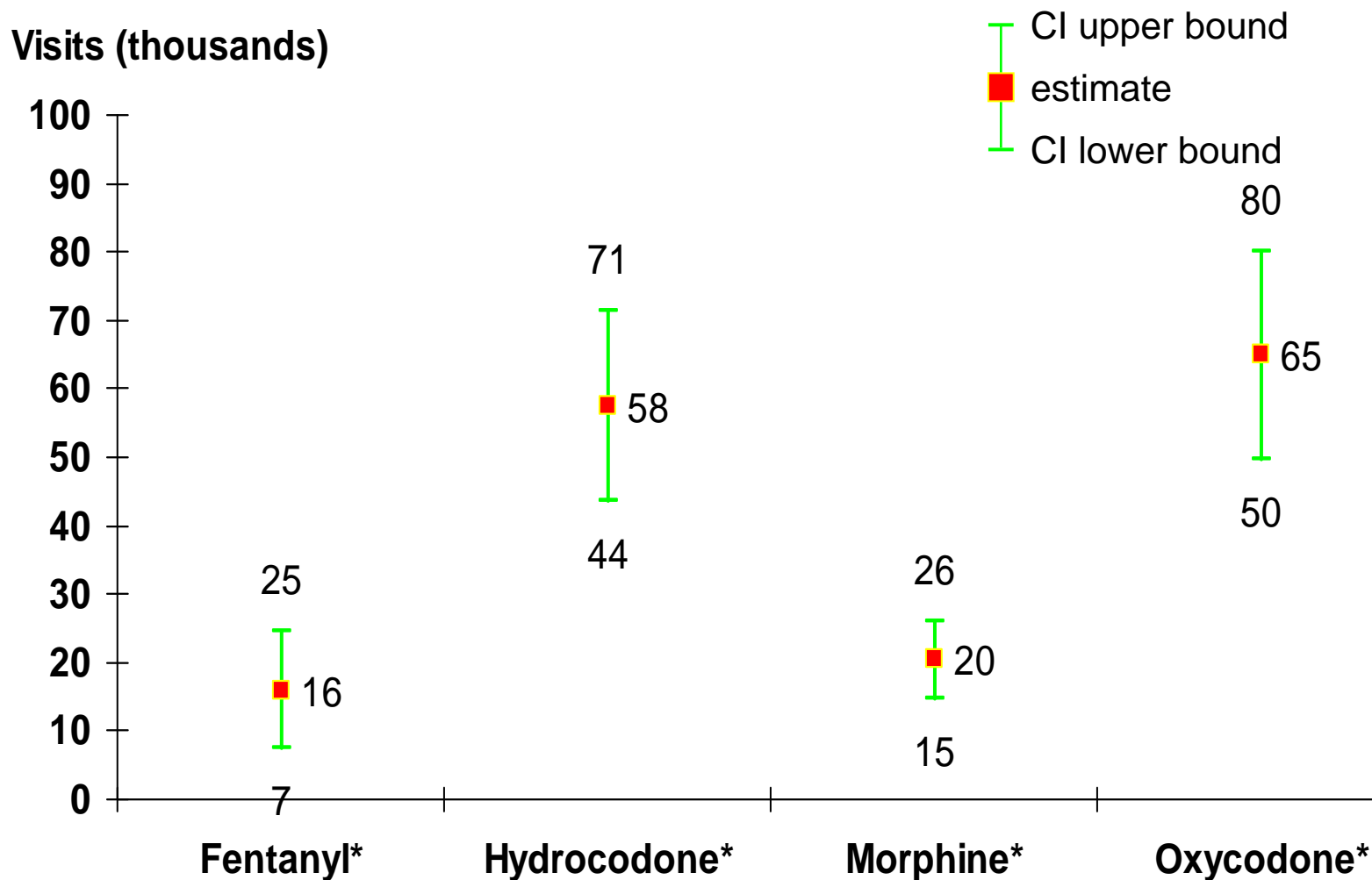
Definition: Nonmedical Use of Pharmaceuticals

- Based on retrospective chart review
 - Exceeded prescribed or recommended dose
 - Used drugs prescribed for another
 - Malicious poisoning
 - Substance abuse
 - Excludes drug-related suicides
 - Includes suicide ideation, plan, gesture

Analysis Domains



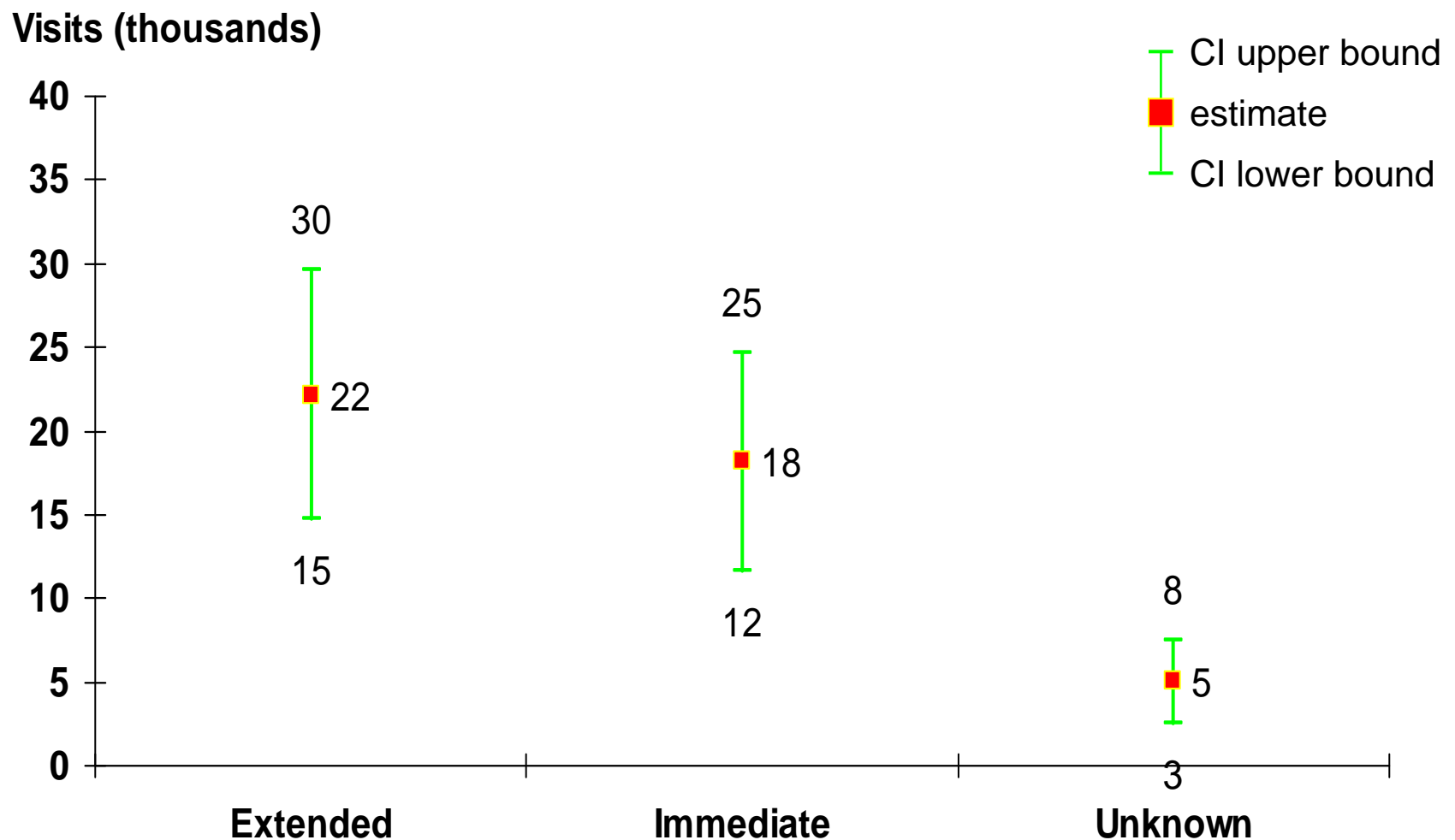
DAWN: Nonmedical Use of Selected Opiates/Opioids, 2006



* Single- & multi-ingredient formulations

Source: National estimates from DAWN, 2006

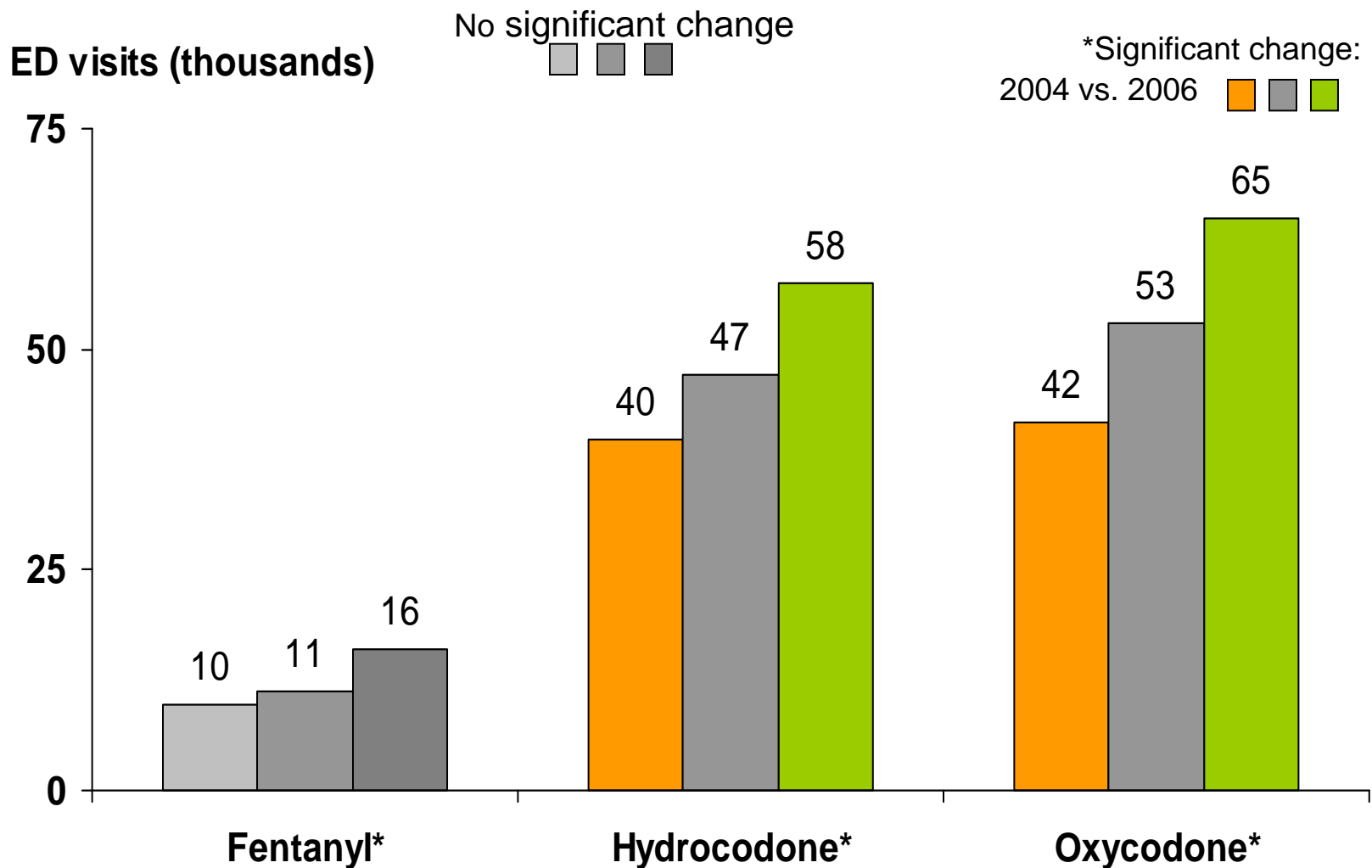
Nonmedical Use of Pharmaceuticals, Oxycodone, by Release Type, 2004



Ratios: Background/Methods

- *Numerator data*
 - Non-medical Use ED Visits (DAWN)
 - Past year non-medical use (NSDUH)
- *Denominator data*
 - Retail prescriptions (Verispan) used as proxy for drug availability
- Calculated estimates per 10,000 retail prescriptions

Numerator: Nonmedical-Use ED Visits: Selected Opiates/Opioids, 2004-2006



* Single- & multi-ingredient formulations

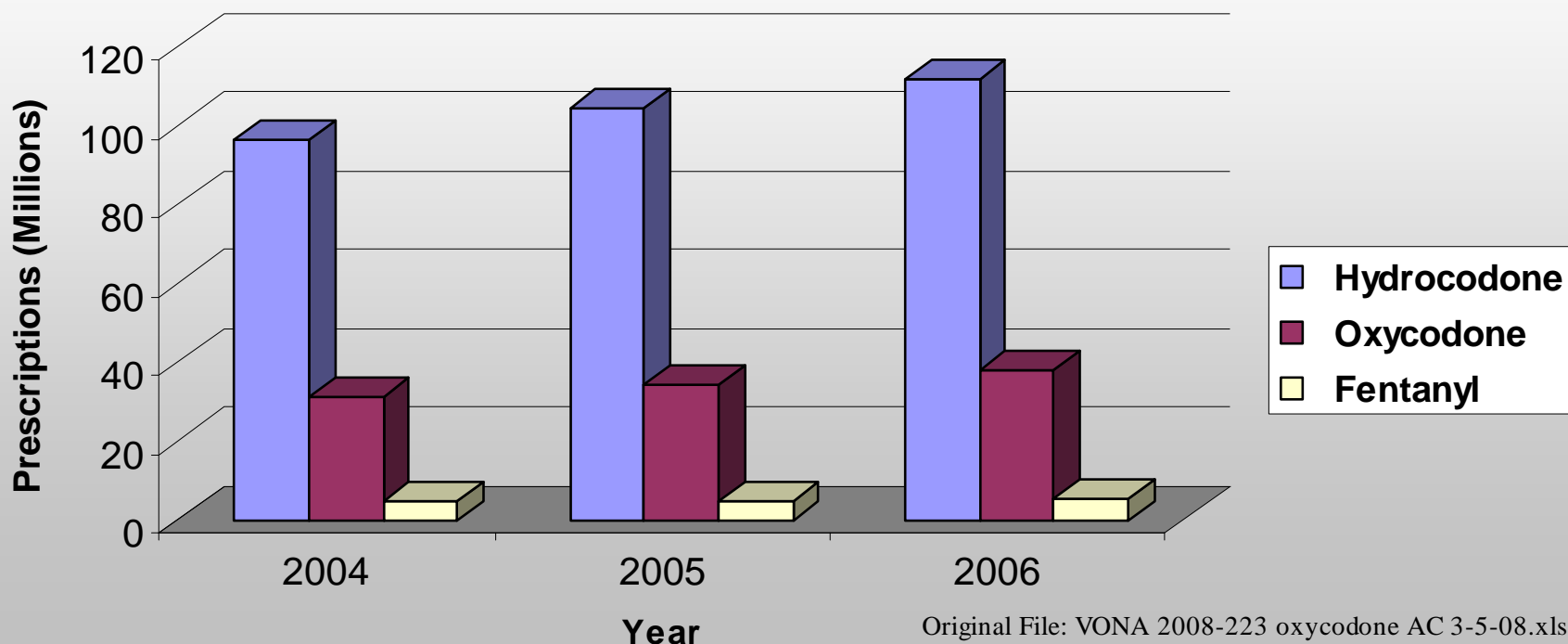
Source: National estimates from DAWN, 2004-2006



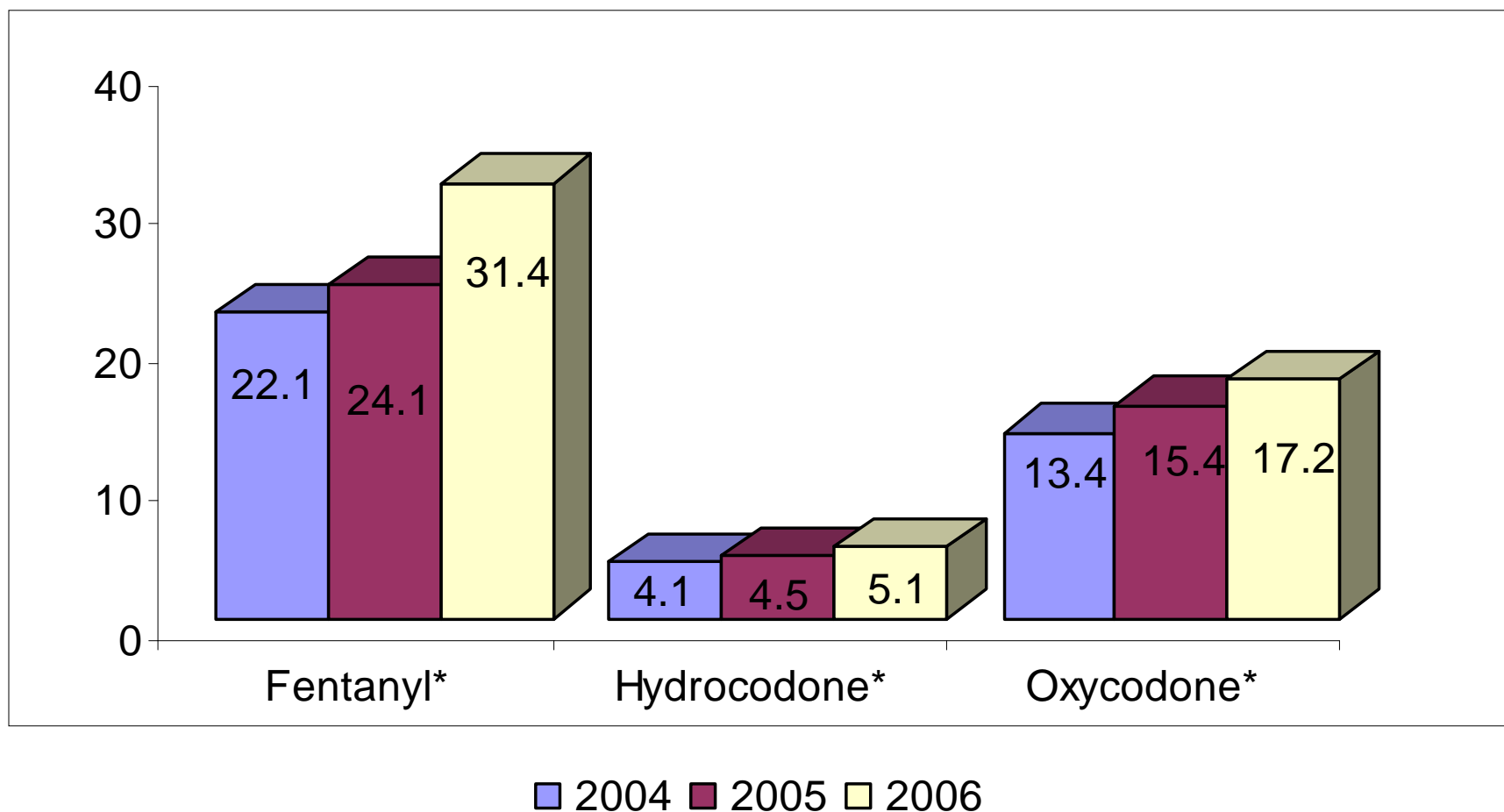
Denominator: Prescriptions Dispensed for Selected Opioids, 2004-2006

Total Retail Prescriptions Dispensed For Hydrocodone, Oxycodone, and Fentanyl Products

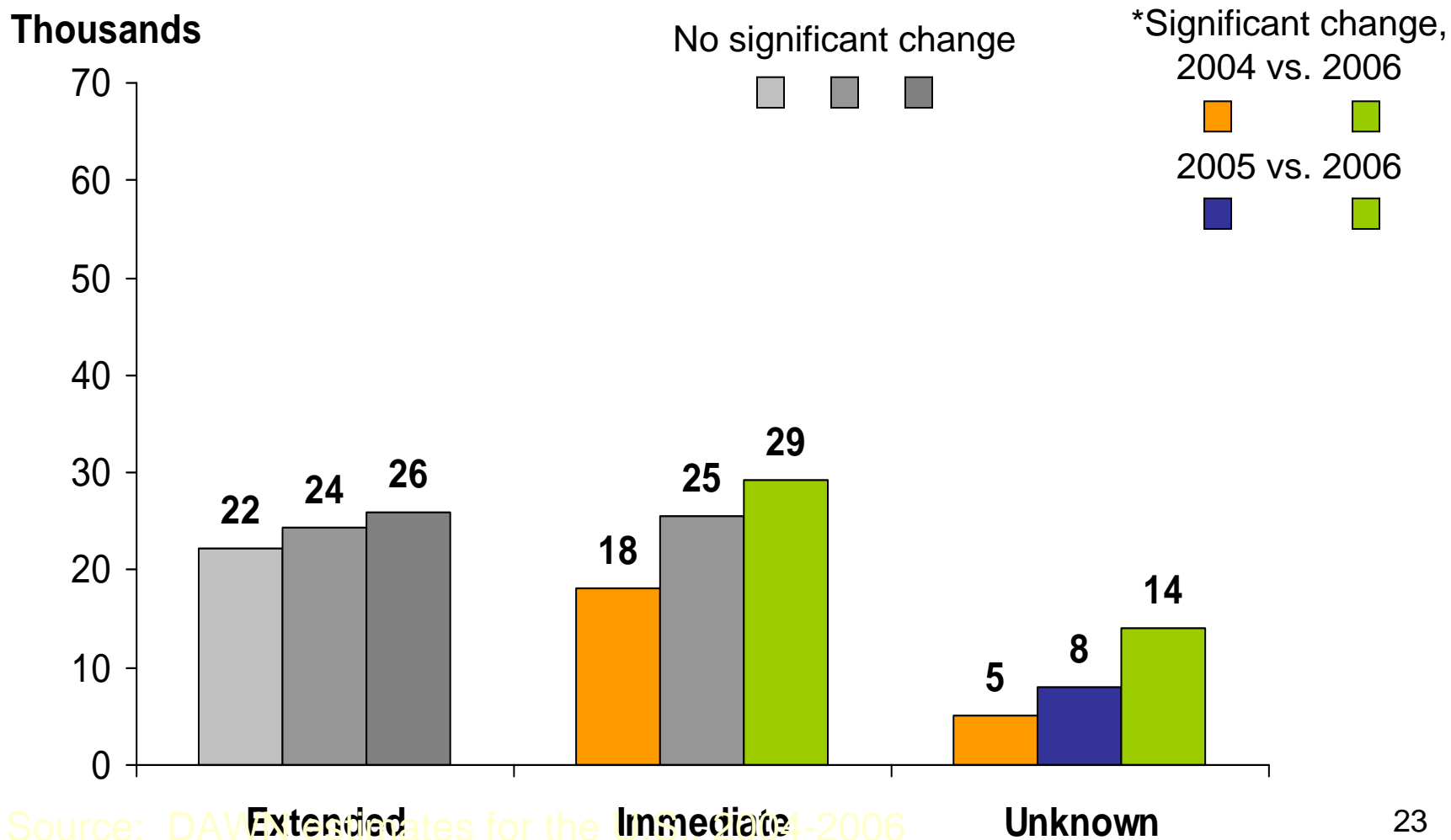
Verispan Vector One™: National (VONA). Extracted 3/2008



Ratios: Non-Medical Use ED Visits per 10,000 Retail Prescriptions, 2004-2006



Numerator: Nonmedical-Use ED Visits: Oxycodone, ER vs. IR

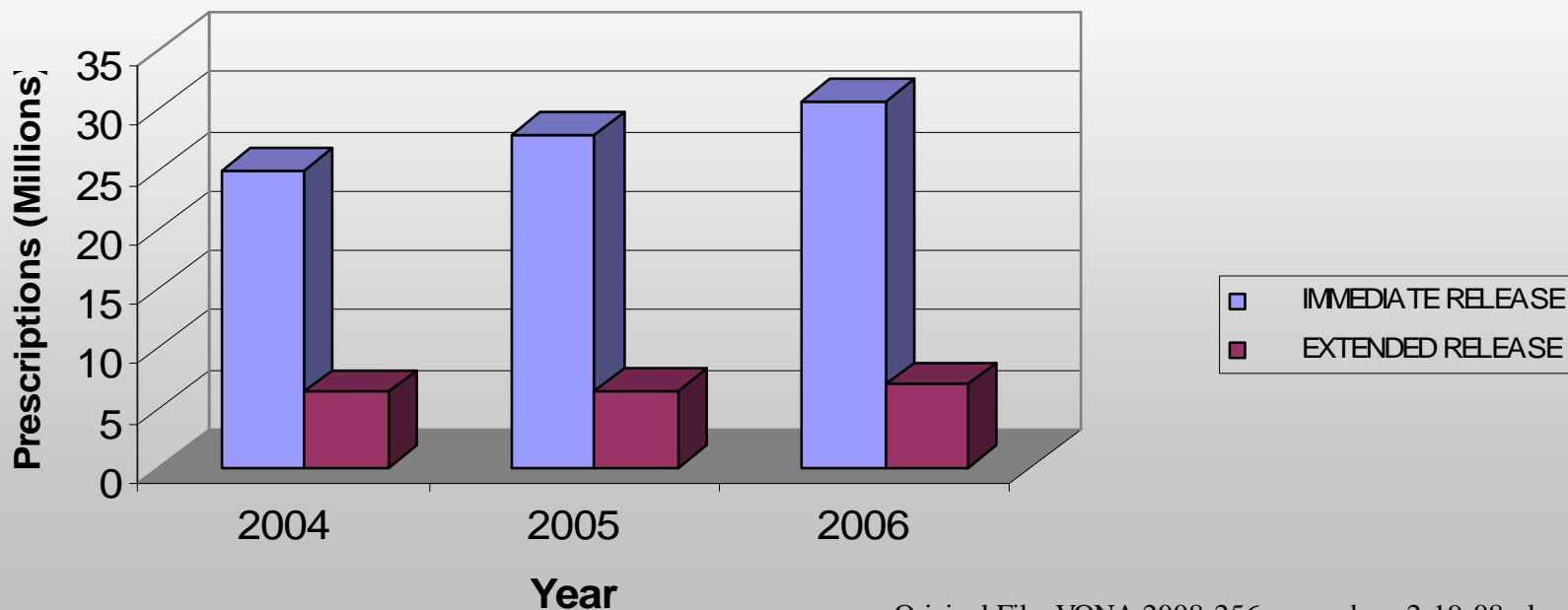




Denominator: Oxycodone Prescriptions by Release Type: 2004-2006

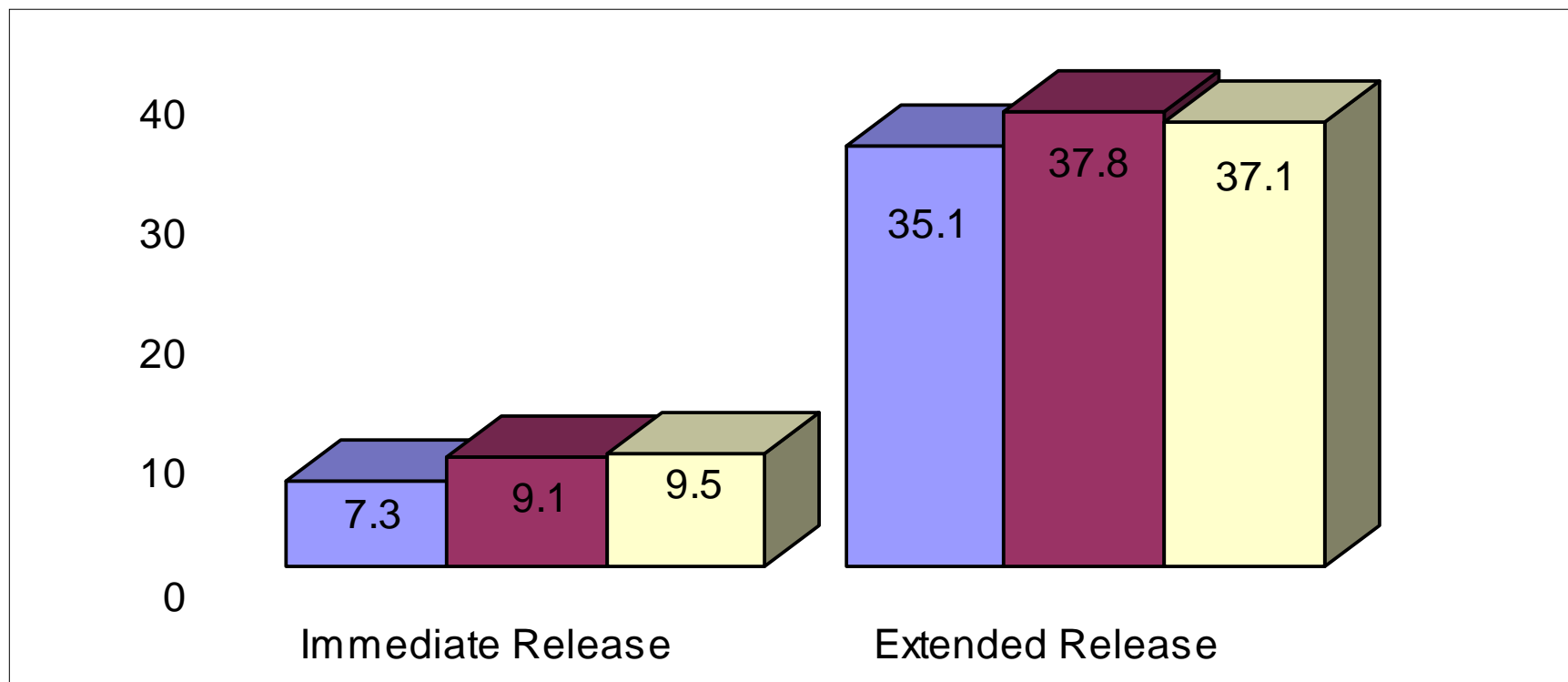
Total Retail Prescriptions Dispensed for Oxycodone 2004-2006

Verispan Vector One™: National (VONA). Extracted 2/2008



Original File: VONA 2008-256 oxycodone 2-19-08.xls

Ratios: ED Visits – Non-Medical Use of Oxycodone per 10,000 Prescriptions by release type, 2004- 2006



Limitations

- Calculating estimates using data from different sources
 - Sampling Methodologies
 - Populations
 - Data are not linked

Summary

- Non-medical use of pain relievers derived from TEDS, NSDUH and DAWN provide information on the public burden of non-medical use of opioids.
- Prescription data can serve as a proxy for drug availability and provides context for non-medical use.
- Ratios of non-medical use of Oxycodone are considerably higher for extended release versus immediate release

Conclusions

- OxyContin and their generics have higher “ratios” of non-medical use than the comparator opioids, hydrocodone, fentanyl and immediate release oxycodone
- Although there has been minimal increases in estimated ratios of Oxycontin non-medical use; actual numbers of users are increasing -- an important public health problem.



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Questions?